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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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7590 07/11/2006			EXAMINER	
SONIA K. GUTERMAN, ESQ. MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C ONE FINANCIAL CENTER BOSTON, MA 02111			STRZELECKA, TERESA E	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/839,658	BRADLEY ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Teresa E. Strzelecka	1637	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 18 April 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14,17,67,68 and 70-72 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14,17,67,68 and 70-72 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. This office action is in response to an amendment filed April 18, 2006. Claims 1-14, 17 and 67-72 were previously pending. Applicants cancelled claim 69 and amended claims 1-5. Claims 1-14, 17, 67, 68 and 70-72 are pending and will be examined.

2. Applicants' amendments overcame the following: objection to claim 69; rejection of claims 1-14, 17 and 67-72 under 35 U.S.C. 112, second paragraph; rejection of claims 1-6, 12, 13, 70 and 71 under 35 U.S.C. 102(b) as anticipated by Cai et al.; rejection of claims 1-6, 12-14, 17 and 67-72 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al.; rejection of claims 7, 8 and 10 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al. in view of Anderson; rejection of claim 9 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al. in view of Anderson and Waggoner et al.; rejection of claim 11 under 35 U.S.C. 103(a) over Kallioniemi et al., McGill et al. and Pollack et al. in view of Ordahl et al. and Anderson.

3. Applicants' arguments are moot in view of new grounds of rejection presented in this office action. The new rejections were necessitated by Applicants' amendment.

### ***Claim Interpretation***

4. Applicants did not define the term "about X bases", therefore, for example, the term "about 30 bases" is interpreted as any number of bases between one and 100, for example. In addition, the phrase "greater than about X bases" is interpreted as any number of bases, as are phrases "smaller than about X bases" and "no more than about X bases".

5. With respect to the term "stringent hybridization conditions", Applicants provided the following description (page 13, lines 14-19 and 29-31; page 14, line 1):

"...The term "stringent conditions" refers to conditions under which a probe will hybridize preferentially to its target subsequence, and to a lesser extent to, or not at all to, other

Art Unit: 1637

sequences. A "stringent hybridization" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization (e.g., as in array, Southern or Northern hybridizations) are sequence dependent, and are different under different environmental parameters." And "...However, the selection of a hybridization format is not critical, as is known in the art, it is the stringency of the wash conditions that set forth the conditions which determine whether a nucleic acid is within the scope of the invention."

Therefore, depending on the length of the nucleic acids participating in the hybridization reaction, different conditions will be considered as being "stringent".

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-6, 12-14, 17, 67, 68 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993).

A) Regarding claim 1, Kallioniemi et al. teach detection gene copy number amplifications or deletions by hybridization of target nucleic acids to an array of plurality of immobilized probes by the method comprising:

(a) providing the plurality of nucleic acid probes comprising a plurality of immobilized nucleic acid segments in an array with each probe at a known location, wherein each probe is a member of a genomic library cloned in a vector, and each probe is the vector having a cloned nucleic acid insert greater than 50 kilobases, wherein the plurality of probes represents all of the chromosome or a genome (Kallioniemi et al. teach CGH (comparative genomic hybridization) arrays (page 2, [0013], [0022]), and DNA arrays in which large-insert genomic clones such as P1, BAC or PAC clones are attached to solid support (page 3, 4 [0053]). Kallioniemi et al. teach an array of clones representing all of the human genome (page 14, [0152], [0153]). Kallioniemi et al. teach an array of P1, BAC or PAC clones each of which has an insert of 80 to 150 kilobases (page 15, [0156]). Kallioniemi et al. teach an array of clones at known locations (Fig. 14).);

(b) contacting the immobilized probes with a sample of target nucleic acid comprising fragments of genomic nucleic acid, wherein said fragments include both strands of a double-stranded genomic DNA fragment and include at least 30% repetitive sequences, and wherein both strands are labeled with a detectable moiety, wherein each labeled fragment consists of a length smaller than 200 bases, and the contacting is under conditions allowing specific hybridization of both strands of the labeled fragment of the target nucleic acid to the probe nucleic acid (Kallioniemi et al. teach contacting genomic DNA target labeled with a fluorescent dye (= detectable moiety) to a CGH array (page 14, [0152]). The target DNA is contacted with the immobilized probes under conditions which permitted specific hybridization of the target to the probes (page 2, [0016]). Kallioniemi et al. teach human genome (page 14, [0153]). Therefore, since human genome contains at least 30% of repetitive sequences, by teaching human genome Kallioniemi et al. inherently anticipate this limitation.); and

(c) observing an amount and location of labeled genomic nucleic acid hybridized to each immobilized probe, to detect regions of amplification or deletion in the sample, wherein positional information of clones on the arrays and chromosomes is correlated, thereby generating a molecular profile of the chromosome or genome of the sample genomic nucleic acid (Kallioniemi et al. teach observation of hybridization events using a CCD camera and detection gene amplifications or deletions on chromosomes (page 2, [0013], [0016]; page 15 [0157], [0160])).).

Regarding claims 12 and 13, Kallioniemi et al. teach hybridization conditions of 42° C and wash of 55° C (page 8, 9, [0100], therefore, according to Applicants' description, they teach stringent hybridization conditions and temperature about 60° C.

Regarding claim 14, Kallioniemi et al. teach target nucleic acid consisting of human DNA (page 14, [0152]).

Regarding claim 17, Kallioniemi et al. teach human genome (page 14, [0153]).

Regarding claims 67 and 72, Kallioniemi et al. teach the sample nucleic acid being chromosome 22 (page 10, [0116]).

Regarding claims 68 and 72, Kallioniemi et al. teach the sample nucleic acid being total human DNA, therefore anticipating the limitations of a sample comprising at least one chromosome and a sample comprising a complete genome (page 14, [0152]; page 15, [0156]).

B) Kallioniemi et al. do not teach DNA fragments with length of less than about 200 bp to less than about 30 bp.

C) Regarding claims 1-6, 70 and 71, McGill et al. teach detection of chromosome 8 amplification using probes derived from the chromosome (col. 3, lines 56-67; col. 4, lines 16). The probe lengths were 10-500 bp (col. 5, lines 35-45 and 52-55), with the optimal probe sequence being about 20 bases (col. 6, lines 1-10). Therefore, since the probes of McGill et al. are shorter

Art Unit: 1637

than 200 bp, the result of using them in hybridization would be less probe aggregation and lower hybridization background, since each of the probes would anneal to a 20 bp sequence which appears once in  $4^{20}$  bp in the genome, or once every 1,099,511,627,776 bp in the genome (as compared to human genome size of 3,000,000,000 bp), that binding of such probes will be very specific, therefore reducing background and non-specific aggregation.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used short probes of McGill et al. in the hybridization method of Kallioniemi et al. The motivation to do so, provided by McGill et al., would have been that probes with about 20 bases allows formation of duplexes which are stable and selective (col. 6, lines 1-3).

Additional motivation for using short probes is provided by Pollack et al., who teach hybridization of DpnII digested and labeled genomic DNAs to cDNA arrays (Abstract; page 46, first paragraph). They found that reducing the size of genomic DNA before labeling improved labeling efficiency by providing greater accessibility of the DNA template following digestion. Such greater accessibility would also allow more specific annealing of the probes to the array.

D) Neither Kallioniemi et al. nor McGill et al. specifically teach double-stranded DNA fragments labeled on both strands.

E) Pollack et al. teach labeling of genomic DNA digested with DpnII and labeling the genomic DNA with a BioPrime labeling kit from GibcoBRL (page 46, first paragraph) for hybridization to a cDNA array. As evidenced by the GibcoBRL catalog, the BioPrime labeling kit contains a DNA polymerase and random primers (page 18-16), therefore, the labeling reaction would result in amplified double-stranded DNA with both strands labeled.

It would have been *prima facie* obvious to have used the BioPrime labeling kit of GibcoBRL to produce double-stranded labeled DNA fragments in the method of Kallioniemi et al., McGill et



Art Unit: 1637

al. and Pollack et al. The motivation to do so is provided by Mackey et al., who teach using the BioPrime kit to label genomic DNA to create probes for hybridization, and teach that probes were prepared from as little as 1 ng of starting material (Abstract), and, as stated by Mackey et al. (page 434, last paragraph):

“In summary, the random primer biotin labeling system described here has a number of attractive features. Small amounts of template DNA (as little as 1 ng) can be amplified and labeled resulting in hundreds of nanograms to microgram of biotinylated probe. This amplification method is especially useful for labeling of DNAs which are difficult to isolate in large quantities; these include YACs, cosmids and DNA isolated from agarose and polyacrylamide gels. The probe size is small and is suitable for in situ hybridization procedures.”

8. Claims 7, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action) and Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993), as applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action).

A) Regarding claim 7, Kallioniemi et al. teach generation of nucleic acids by polymerase chain reaction, nick translation or random priming (page 10, [0114]-[0116]).

Regarding claim 8, Kallioniemi et al. teach labeling of nucleic acid fragments by nick translation or random priming (page 10, [0116]).

B) Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. do not teach fractionation of DNA by DNase digestion.



Art Unit: 1637

C) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNase I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used DNase I digestion of Anderson to fragment genomic target DNA in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Anderson, would have been that DNase I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNase I in the reaction (page 3019, first two paragraphs).

9. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action), as applied to claim 8 above, and further in view of Waggoner et al. (U. S. Patent No. 5,268,486; cited in the previous office action).

A) Claim 9 is drawn to the label comprising Cy3 or Cy5.

B) Kallioniemi et al. and McGill et al. teach fluorescent labels, but do not teach Cy3 or Cy5.

C) Waggoner et al. teach luminescent cyanine dyes, including Cy3 and Cy 5 (col. 19, formula at the bottom; claim 8; Cy3 has  $m=1$ , Cy5 has  $m=2$ ). The dyes are be used to label nucleic acids (col. 2, lines 58-61; col. 4, lines 29-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the cyanine dyes of Waggoner et al. in the method of Kallioniemi et al.,

Art Unit: 1637

McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Waggoner et al., would have been that cyanine dyes were used for detecting mixtures of components because they had a wide range of excitation and emission wavelengths (col. 4, lines 36-49).

10. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kallioniemi et al. (US 2002/0132246 A1; cited in the previous office action), McGill et al. (US 5,658,730 A; cited in the previous office action), Pollack et al. (Nature Genetics, vol. 23, pp. 41-46, September 1999; cited in the previous office action), as evidenced by GibcoBRL Catalog (pages 18-15 and 18-16, 1995-96), and Mackey et al. (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991; cited in the previous office action), as applied to claim 1 above, and further in view of Ordahl et al. (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976; cited in the previous office action) and Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981; cited in the previous office action).

A) Claim 11 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNase digestion.

B) Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. do not teach fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNase digestion.

C) Ordahl et al. teach fragmentation of genomic DNA in preparation for DNA hybridization experiments. Ordahl et al. teach that it is advantageous to use DNA fragments of less than 500 bp in hybridization experiments (page 2985, first paragraph). Ordahl et al. teach that DNA fragmented in French press had an average size of 230 base pairs (Abstract; page 2986; Fig. 4). Ordahl et al. do not teach DNase I fragmentation after shearing.

Art Unit: 1637

D) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNase I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used shearing of Ordahl et al. and DNase I digestion of Anderson to fragment genomic target DNA in the method of Kallioniemi et al., McGill et al., Pollack et al. and Mackey et al. The motivation to do so, provided by Ordahl et al. and Anderson, would have been that it was advantageous to use short DNA fragments in hybridization (Ordahl, p. 2885, first paragraph) and that DNase I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNase I in the reaction (Anderson, page 3019, first two paragraphs).

11. No claims are allowed.

### ***Conclusion***

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka  
Primary Examiner  
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7/8/07